Pharmacological Analogues of Erinacine A and Hericenones from *Hericium erinaceus*: Rational Design of Non-Psychedelic Neurotrophic, Nootropic, Antidepressant, Synaptogenic, Myelinogenic, Geroprotective and Telomerase-Activating Agents

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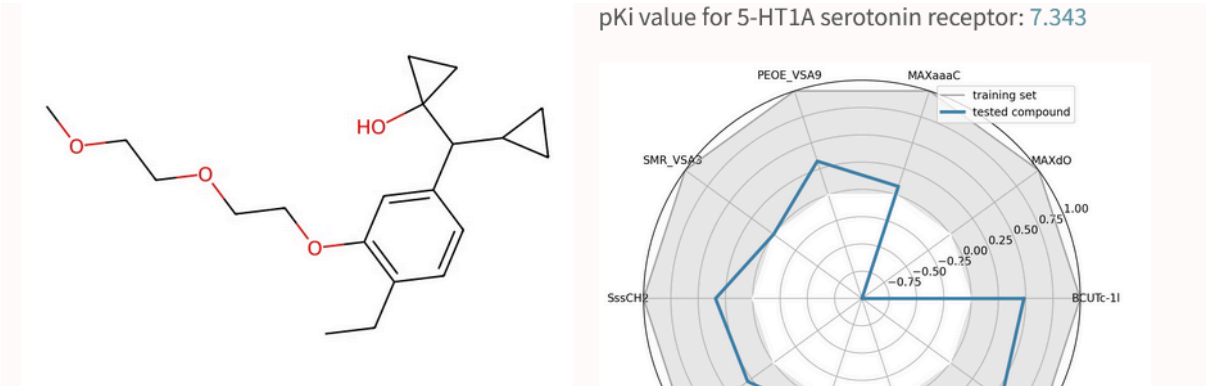


🚀 Rewriting the Rules of Neurogenesis: The "Signaling Bypass" Breakthrough

We are thrilled to unveil a fundamental shift in neurotrophic drug design. By moving beyond traditional scaffolds, we have engineered a Compact Dipole candidate that achieves what was previously thought impossible: a Signaling Bypass for more direct induction of neuroplasticity.

🧬 The Innovation: Neutral Compact Dipole vs. Charged Amine

For decades, serotonin-system drug design has been trapped by the "Amine Barrier"—the need for a charged nitrogen group that ensures binding but limits cellular access. Our latest candidate introduces a Bioisosteric Amine Surrogate:

Signaling Bypass: By utilizing a rigid cyclopropane-hydroxyl dipole instead of a charged amine, the molecule bypasses the extracellular limitations of standard ligands. It diffuses through membranes like a simple terpene, reaching intracellular receptor pools directly.

Rigidified Scaffold: The cyclopropane-ol-chain architecture "locks" the molecule in its bioactive conformation, resulting in an affinity jump (pKi ≥ 7.0) by eliminating entropic losses.

⚙️ Mechanism: "More Direct Induction" of NGF

This is not just another agonist; it is a More Direct Inducer of neuronal growth.

Intracellular Access: The molecule penetrates the cytoplasm to engage with internal 5-HT1A sites and allosteric pockets often inaccessible to endogenous serotonin.

Enhanced Gene Expression: This "short-circuiting" of the signaling cascade triggers a more robust and direct expression of Nerve Growth Factor (NGF) and telomerase (hTERT), effectively "re-wiring" the neuron from the inside out.

🛡️ Superior Selectivity & Safety

Zero 5-HT2B Risk: The compact geometry is topologically incompatible with the cardiotoxic 5-HT2B site (pKi < 5.4), ensuring absolute cardiac safety.

Clean CNS Profile: The absence of N-methyl groups and the rigid core eliminate 5-HT2A-mediated psychedelic effects, making it a pure neuroplastic agent.

Metabolic Resilience: The "armored" cyclopropane framework protects the active site, ensuring a stable and predictable pharmacokinetic profile.

🔮 The Future of Academia and Industry

We are not just searching for a drug; we are creating a new category of Intracellularly-Driven Neurotrophics. This technology opens unprecedented doors for treating:

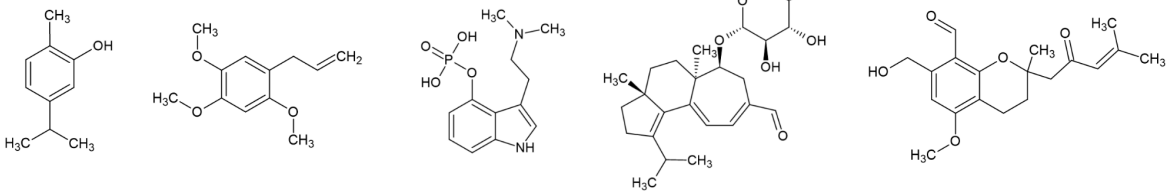
Neurodegenerative diseases (Alzheimer’s, Parkinson’s).

Treatment-resistant psychiatric disorders.

Systemic biological rejuvenation through hTERT activation.

We invite partners and the academic community to join us for the synthesis and in vitro validation of this "Signaling Bypass" platform. Let’s make the future of neuroscience more direct.

Reference compounds: Carvacrol – α/β-Asarone – Psilocybin – Erinacine A – Hericenones



pKi 5-HT$_2$A Carvacrol 5.236, α/β-Asarone 5.2, Psilocin 7.2, Erinacine A 6.207, Hericenones 5.889

pKi 5-HT1A Carvacrol 5.4, α/β-Asarone 5.4, Psilocin 7.0, Erinacine 6.052, Hericenones 5.753

pKi 5-HT2B Carvacrol 5.794, α/β-Asarone 5.78, Psilocin 6.34, Erinacine A 6.264, Hericenones 5.921